REMARKS

Claims 1-14 are pending in the present application. Claims 1-3 have been amended. Support for newly amended claims can be found throughout the specification as filed. Specifically, support for the amendments to claims 1-3 can be found at least at page 5, line 30 of U.S. serial number 08/109,393, to which the present application claims priority, the entire contents of which were incorporated by reference (see page 1, lines 10-11 of the instant application). No new matter has been added.

Amendment or cancellation of claims should in no way be construed as an acquiescence, narrowing, or surrender of any subject matter. Amendments or cancellations have been made not only to point out with particularity and to claim the present invention, but also to expedite prosecution of the present application. Applicants reserve the option to prosecute the originally filed claims further, or similar ones, in the instant or subsequently filed patent applications.

Advisory Action

Applicants filed an Amendment and Response to the Final Office Action on January 17, 2008. In response, the Examiner mailed an Advisory Action on March 17, 2008 indicating that some of the previous rejections of record were maintained and that the amendment and response to the Final Office Action had not been entered.

As indicated in the Advisory Action, the Examiner has maintained the rejection under 35 U.S.C. § 112, First Paragraph, because according to the Examiner, "the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity." The Examiner further states, "the instant specification fails to provide a disclosure of which residues are required for the B7-2 molecule and fragments thereof that would retain the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 in B7-2 molecules and fragments thereof" (page 2 of Advisory Action).

Applicants traverse the foregoing rejections and submit that based on the teachings in the instant specification and incorporated references, one of ordinary skill in the art would find the disclosure clear and adequate. Applicants have amended claims 1-3 to recite, "at least 100 contiguous amino acids of SEQ ID NO:2 or 4." Support for these claim amendments can be

found, at least, at page 5, line 30 of U.S. Serial Number 08/109,393, which was expressly incorporated by reference into the instant application. For example, the specification recites "[p]eptides having B7-2 activity and consisting of at least…100 amino acid residues in length."

Furthermore, Rennert *et al.* (International Immunology, 1997, copy of which is provided herewith as Appendix A) teach that the IgV domain (*e.g.*, approximately 100 amino acids in length) of B7-2 is sufficient to co-stimulate T cells. Indeed, Rennert *et al.* state, "only the IgV domain of B7-2 was required for binding" (pages 807-808, sentence bridging pages) to CD28 and CTLA-4. Rennert *et al.* also disclose that, "[t]he B7-2 IgV domain extended from amino acid 23 (alanine) to 133 (leucine)" (page 806, left col.), thus, it is clear that 100 contiguous amino acids of SEQ ID NO:2 or 4 would have the activity as instantly claimed. In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections.

Acknowledgement of Species Election

On page 2 of the Office Action dated February 7, 2007, the Examiner incorrectly acknowledged Applicants' alleged election of the species "anti-inflammatory agents, and aspirin." In Response to the Office Action, filed August 7, 2007, Applicants respectfully pointed out that provisional election of the species "B7-2 encoding nucleic acids without additional molecules" and "sarcoma" were made, for search purposes only, in the Response to Restriction Requirement mailed on November 6, 2006. Applicants also requested that the Examiner acknowledge the correct election of species. However, the correct election of species was not acknowledged in the instant Office Action. Therefore, Applicants again respectfully request that the correct election of species be acknowledged.

Rejection of Claims 1-3 and 6-14 Under 35 U.S.C. § 112, First Paragraph: Written Description

The Examiner has rejected claims 1-3 and 6-14 under 35 U.S.C. § 112, first paragraph, as allegedly not meeting the written description requirement. Specifically, the Examiner contends that there is insufficient written description for the genus set forth in claims 1-3, and claims dependent thereon. In rejecting the claims, the Examiner reiterates the references and arguments from the Office Action mailed February 7, 2007, and further cites *University of Rochester v.*

G.D. Searle & Co., 358 F.3d 916, 69 USPQ2d 1886 (Fed. Cir., 2004) as allegedly supporting the position that "disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity."

Applicants respectfully traverse the rejection. As the Examiner is aware, "a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." Moreover, "[t]he examiner has the initial burden of presenting a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." Further, "[i]n rejecting a claim, the examiner must set forth express findings of fact which support the lack of written description conclusion." Finally, "[a] general allegation of 'unpredictability in the art' is not a sufficient reason to support a rejection for lack of adequate written description" (all quotations in this paragraph from MPEP 2163.04).

Claims 1-3 teach specific sequences (SEQ ID NO: 2 and 4) that recite particular chemical structures. The specification and priority documents (incorporated by reference in their entireties) are replete with teachings of the functional characteristics of the molecules encoded by the nucleic acids used in the claimed methods, including the "ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 ligand," as recited in claims 1-3. Hence, Applicants clearly teach the structural and functional characteristics of the claimed nucleic acids.

Applicants also teach a correlation between chemical structure and function, by using the chemical structure and function of human B7-2 to isolate and characterize murine B7-2 (see Example 6 of the amended specification, incorporated by reference from U.S.S.N. 08/280,757, now U.S. Patent No. 6,130,316). Example 6 shows that the structural and functional information gained during the isolation of human B7-2 can readily be applied to isolate B7-2 from other species - in this case the mouse. Specifically, CTLA4-Ig and CD28-Ig were used to isolate B7-2 expressing cells, and an anti-B7-1 monoclonal antibody (mAb) was used to remove B7-1 expressing cells. These detailed methods demonstrate that the structural characteristics and functional criteria defined in the claims are sufficient to isolate and define B7-2 molecules that are at least 50% homologous, and that B7-2 can readily be distinguished from the related family member B7-1. A person of ordinary skill in the art would thus readily recognize that methods that are essentially identical to those used in Example 6 could also be used to isolate other B7-2

species and, hence, that the claimed methods fall well-within the scope of the written description provided in the specification.

In *University of Rochester v. G.D. Searle & Co.*, the claimed methods in the patent at issue required "administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment" (U.S. Patent No. 6,048,850; "the '850 patent"). However, the '850 patent did not disclose any compounds that could be used in the claimed methods, nor was a single compound that could be used in the claimed methods known at the time of filing. This is clearly not the case in the instant application, where Applicants have taught a representative number of species having the structure and properties of the B7-2 nucleic acids recited in the claimed methods, as well as detailed methods for the isolation of other B7-2-encoding nucleic acids of the claimed methods.

The Examiner cites *Fiers v. Revel*, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) as supporting the position that "[a]dequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it" (quotation from the Examiner, emphasis added, page 5, paragraph 6 of the instant Office Action). The method presented in Example 6 of U.S.S.N. 08/280,757 is not merely a "potential" method for isolating other species of B7-2 molecules, but a proven method that is sufficiently robust to isolate B7-2 family members with approximately 50% homology to each other. Hence, Applicants clearly provide a level of written description far exceeding "a potential method for isolating" the claimed B7-2 molecules. Contrary to the Examiner's position, in *Fiers v. Revel*, the court found that the enablement requirement was satisfied for a claim directed to DNA encoding a protein where the specification "sets forth a detailed teaching of a method for obtaining a DNA coding" for the protein. Example 6 clearly fulfills this requirement.

In *Amgen Inc. v. Chugai Pharm. Co.*, the court found claim 7 of U.S. Patent No. 4,703,008 (the '008 patent) invalid for lack of enablement (not written description). Claim 7 of the '008 patent is directed to a DNA sequence encoding a polypeptide with an amino acid sequence "sufficiently duplicative of that of erythropoietin" to possess a number of functional properties. The claim does not recite any degree of homology, as recited in the instant claims. Furthermore, in contrast to the instant specification, the exemplification in the '008 patent

included "the gene and a handful of analogs whose activity has not been clearly ascertained." In contrast, Applicants have provided specification of structure and exemplification of analogs having the required bioactivity that clearly exceeds the disclosure found in the '008 patent.

Similarly, in *Fiddes v. Baird*, 30 USPQ2d 1481, exemplification of a single bovine fibroblast growth factor (FGF) sequence was used as a basis for claims directed to the genus of mammalian FGF sequences. However, the priority document at issue in *Fiddes v. Baird* (U.S.S.N. 06/747,154, now U.S. Patent No. 4,956,455) contained no exemplification of methods that could be used to isolate FGF from other mammalian species. This is in sharp contrast to the detailed exemplification contained in the instant application and priority documents, which not only teach more than one species of B7-2, but also provide detailed and proven methods for the isolation of B7-2 molecules from additional species.

The Examiner then cites five references which allegedly provide support for the contention that the correlation between the structure and function of B7 molecules, and proteins in general, is unpredictable. Citing Riley *et al.* (*Blood*, 2005, 105:13-21), the Examiner states that "different molecules having sequence similarity to molecules such as B7-1 and B7-2 have different, and often opposite functions." Applicants respectfully point out that Riley *et al.* focuses on the different responses elicited by the different members of the CD28 family of receptors, including CD28, CTLA-4, ICOS, PD-1, and BTLA. In this context, a particular B7 protein may elicit a different response, depending on which receptor it binds. Riley *et al.* does not disclose that the differences in the responses are related to the degree of similarity (or lack thereof) between B7 molecules. Moreover, Riley *et al.* provides no disclosure of any B7 molecules having sequence identity at the claimed level of "at least 50% homologous" and "opposite functions." Hence, Riley *et al.* provides no evidence to support the contention that a person of ordinary skill in the art would not recognize that Applicants were in possession of the claimed invention.

In citing the disclosure of Coyle *et al.* (*Nature Immunology*, 2001, 2: 203-209), the Examiner states that "B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics." This statement supports Applicants' position that the claimed methods, directed to using nucleic acids encoding B7-2 molecules, are sufficiently distinct from methods using nucleic acids encoding other B7 family members, and that the nucleic acids in the instant claims

are readily identifiable and characterized as B7-2 encoding nucleic acids. Coyle *et al.* further discloses that the closely related family members "B7-1 and B7-2…exhibit 25% identity in the Ig-variable (V) and constant (C) like extracellular domain." The level of homology required in the instant claims is "at least 50%," a level at which the nucleic acids would be readily identifiable as B7-2 encoding nucleic acids. Coyle *et al.* thus supports Applicants' position that a skilled artisan would readily recognize that Applicants were in possession of the invention defined by the claims.

The Examiner then cites Metzler *et al.* (*Nature Structural Biology*, 1997, 4: 527-531) to provide support for the contention that single amino acid changes can result in alterations in the function of proteins. Metzler *et al.* discloses that certain mutations can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86. Applicants respectfully point out that the nucleic acids of the instant claims must encode polypeptides that satisfy particular functional requirements, namely "the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 ligand." Applicants teach the extracellular and variable domain portions of the B7-2 protein (see the amended specification and throughout priority document U.S.S.N. 08/280,757). Applicants also teach that mutations can be introduced into the DNA sequences encoding B7-2 molecules (see, for example, the current amendments to the specification). Applicants provide various assays to screen for proteins having B7-2 activity, including the ability to bind CTLA4-Ig and CD28-Ig, while not binding anti-B7-1 antibody, and costimulatory activity toward T cells (Example 6). Given the detailed structural and functional information contained within the specification and priority documents, as well as the assays taught for screening for B7-2 activity, one of ordinary skill in the art would readily recognize that Applicants were in possession of the claimed invention at the time of filing.

The Examiner then cites Attwood (*Science*, 2000, 290: 471-473), stating that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." Applicants respectfully point out that this position is in contrast to Riley *et al.* (cited by the Examiner, above), which states that "most of the B7 family member ligands were discovered by homology searches" (page 13, column 1, lines 11-13). Applicants further point out that the nucleic acids recited in the instant claims are not identified "merely on the basis of some degree of similarity," but are identified by (1) a degree of homology that clearly distinguishes B7-2 from other B7 family members, and (2) particular functional characteristics,

namely "the ability to costimulate a T cell and the ability to bind CD28 or CTLA4 ligand." One of ordinary skill in the art would thus readily recognize that Applicants were in possession of the claimed invention at the time of filing.

Finally, in citing Skolnick *et al.* (*Trends in Biotechnology*, 2000, 18: 34-39), the Examiner states that "in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein." As discussed *supra*, Applicants have performed ample experimentation to determine the function of structurally related B7-2 proteins, in particular human and murine B7-2. Given the structural and functional information taught in the specification, as well the assays taught for screening for B7-2 activity, one of ordinary skill in the art could readily isolate the claimed B7-2 nucleic acids.

In light of all of the foregoing, neither the cited case law nor other references provide "a preponderance of evidence why a person of skill in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims" (emphasis added, MPEP 2163.04). Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 1-3 and 6-14 Under 35 U.S.C. § 112, First Paragraph: Enablement

The Examiner has rejected claims 1-3 and 6-14 under 35 U.S.C. § 112, first paragraph, as allegedly not enabling the nucleic acids recited in claims 1-3. Specifically, the Examiner states that:

> the instant specification does not provide sufficient guidance that would steer the skilled artisan towards those 'B7-2 molecules and fragments thereof, particularly as to those nucleic acid / amino sequences with limited sequence or sequence homology responsible for retaining the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4' that could be used to carry out the claimed methods… *(emphasis in original, page 9, paragraph 5 of the instant Office Action)*

Applicants respectfully traverse the rejection. As discussed above, Example 6 contains ample guidance that would steer the skilled artisan toward B7-2 molecules with the claimed sequence homology and functional properties. This is not a prophetic example, Applicants have demonstrated that this method actually works. A person of ordinary skill in the art would readily recognize that the method could be used to isolate nucleic acids encoding other B7-2 molecules. Therefore, the degree of enablement provided by the Applicants is not merely limited to "a starting point from which one of skill in the art can perform studies with the known B7-2 molecules to practice the claimed invention" (emphasis in original; page 10, paragraph 3 of the instant Office Action). As discussed *supra*, Applicants have clearly enabled methods that would clearly lead to the isolation of other B7-2 molecular species.

The Examiner then proceeds to cite the same journal articles cited in the foregoing rejection under 35 U.S.C. § 112, first paragraph (written description), to allegedly demonstrate that Applicants have not provided an enabling disclosure of the recited nucleic acid molecules. Applicants respectfully incorporate by reference the arguments advanced above.

Finally, the Examiner cites two additional cases that allegedly support his position: In *Colbert v. Lofdahl*, 21 USPQ2d, 1068 (BPAI 1992), it was found that "[i]t is not sufficient to define the recombinant molecule by its principal biological activity." Applicants respectfully point out that the nucleic acids of the instant claims are defined by their structure and biological activity.

The Examiner then cites *Genentech Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 42 USPQ2d 1001 (Fed. Cir. 1997), where the court found that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required." As outlined in Example 6, Applicants have clearly provided specific starting materials and conditions under which a process can be carried out to obtain the nucleic acids of the instant claims. In light of all of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection.

Double Patenting Rejections

The Examiner has provisionally rejected claims 1-14 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of issued U.S. Patent No. 6,723,705. Applicants respectfully request that the Examiner hold in abeyance all obviousness-type double patenting rejections based on said issued U.S. patent until allowable subjected matter is indicated, at which point Applicants will consider filing a terminal disclaimer.

CONCLUSION

Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at (617) 832-1000. If any fees are due, the Commissioner is hereby authorized to credit any overpayment or charge any deficiencies to **Deposit Account No. 06-1448, Reference No. WYS-018.04.**

Respectfully submitted,
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